Using Helium Leak Detection CCI Testing to Inform Container Closure System Design

A Prefilled Syringe Case Study

Container Closure Integrity: Regulations, Test Methods, Application

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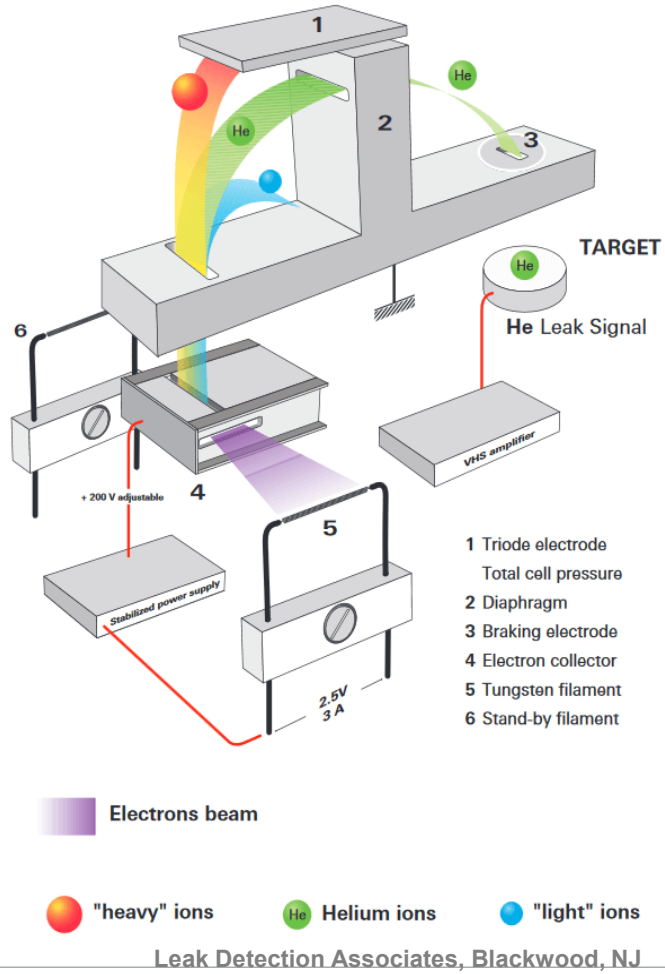
Outline

- Overview of Helium Leak Detection (HeLD)
- Method development for syringes
  - Fixture design
  - Helium charging
- Applications of Helium Leak Detection
  - Determination of inherent package integrity
  - Evaluation of syringe system and sub-system design
  - Assessment of container closure robustness

Introduction – Helium Leak Detection

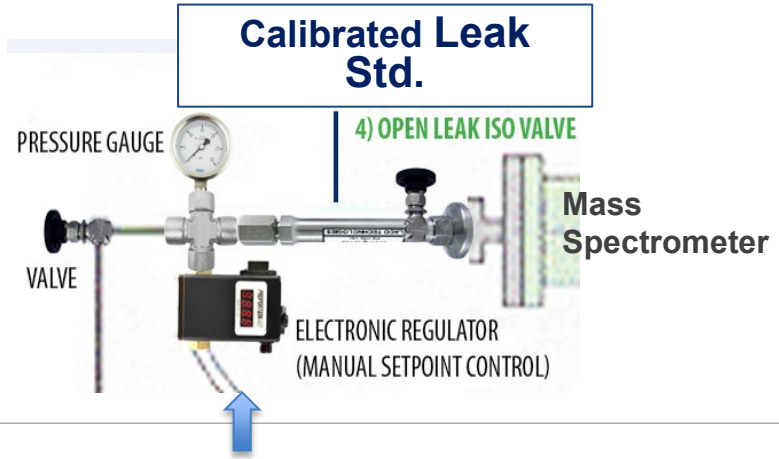
- **Selectivity**
  - Low atmospheric interference: Helium in the atmosphere (~5 ppm)
  - Do need to minimize lab ambient helium and permeation
- **Flows through cracks ~2.7x faster than air**
- **Sensitivity & Quantitative**
  - Mass spectrometer as detector



Leak Detection Associates, Blackwood, NJ

Instrument Capability

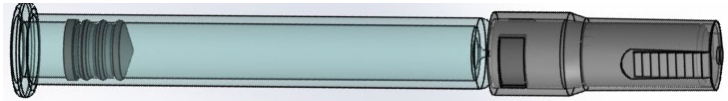
- **Calibration**
  - Internal calibration standards
  - Quantitation Range: 1x10-11 to 1x10-3 atm-cc/sec
- **System suitability**
  - NIST-traceable standard leaks
  - Verified range: 4x10-10 to 6x10-4 atm-cc/sec
- **Results reported as helium leak rate**
  - Converted to a nominal leak orifice size using USP <1207> method, where appropriate



Purpose

- **Quantitatively determine inherent package integrity**
  - The leakage rate (or the equivalent leak size) of a well-assembled package using no-defect components. Inherent package integrity is a measure of the leak tightness of a container–closure system, given anticipated variables of material composition, dimension, processing, assembly; package storage, distribution and use. (USP<1207>)
- **Demonstrate conformance to Maximum Allowable Leakage Limit (MALL)**
  - To preserve sterility and product formulation content
    - MALL <= 6x10-6 mbar·L/s (atm-cc/sec) (USP<1207>)
- **Inform packaging system design and process development**
  - Assess critical seal elements, sub-systems, and system design
  - Evaluate sealing robustness (e.g. impact of potential defects on package integrity)

Prefilled Syringe System

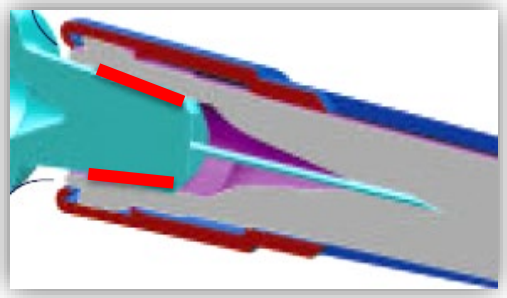


Drug Product Compartment

- Plunger-barrel seal
- Needle shield seal
  - Needle tip seal
  - Glued needle stem

Needle Stem Compartment

- Needle shield/syringe head

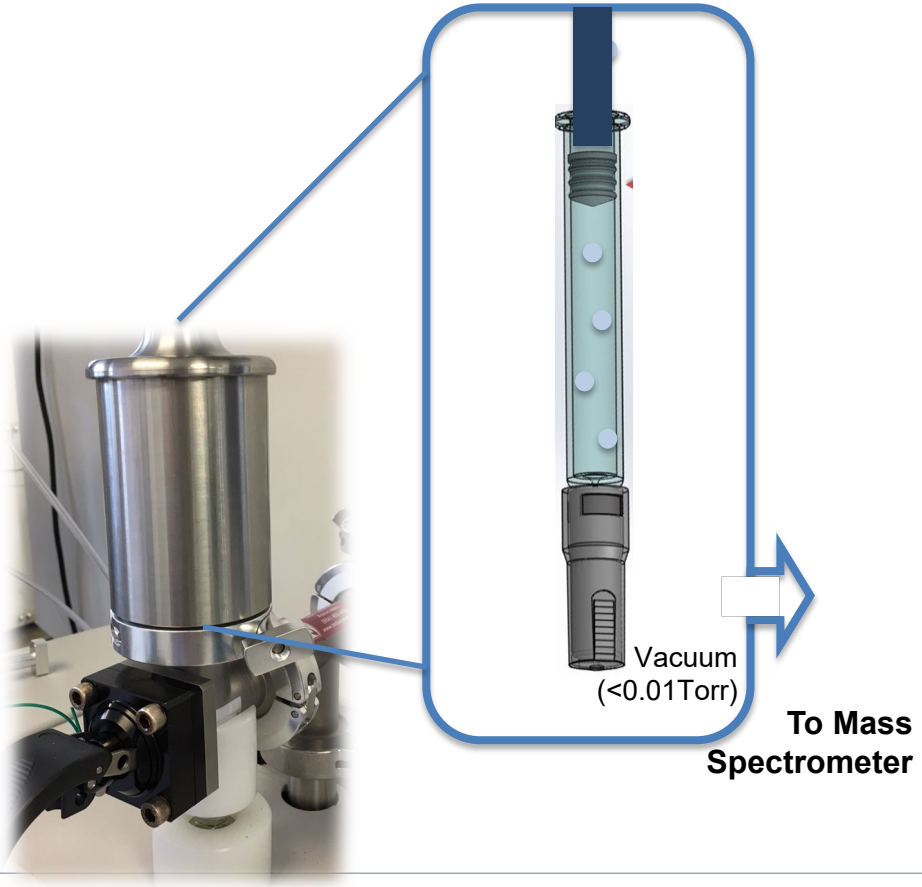


Preliminary Testing

1. **Filling**: syringes charged with helium and plungered in a glove box

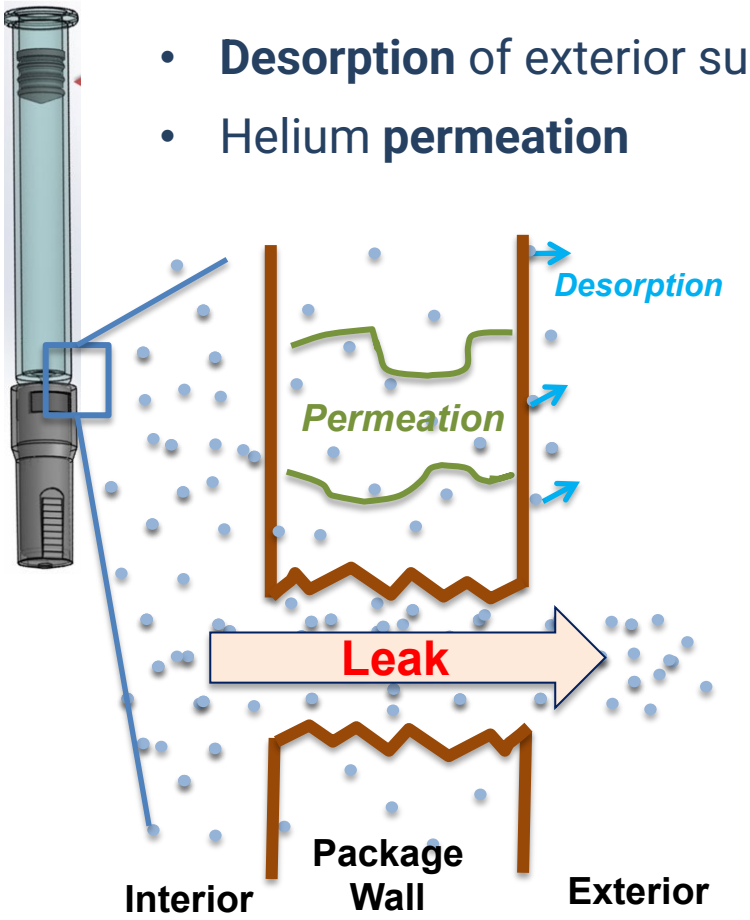
2. **Testing**: filled syringe is placed in a sample chamber for testing

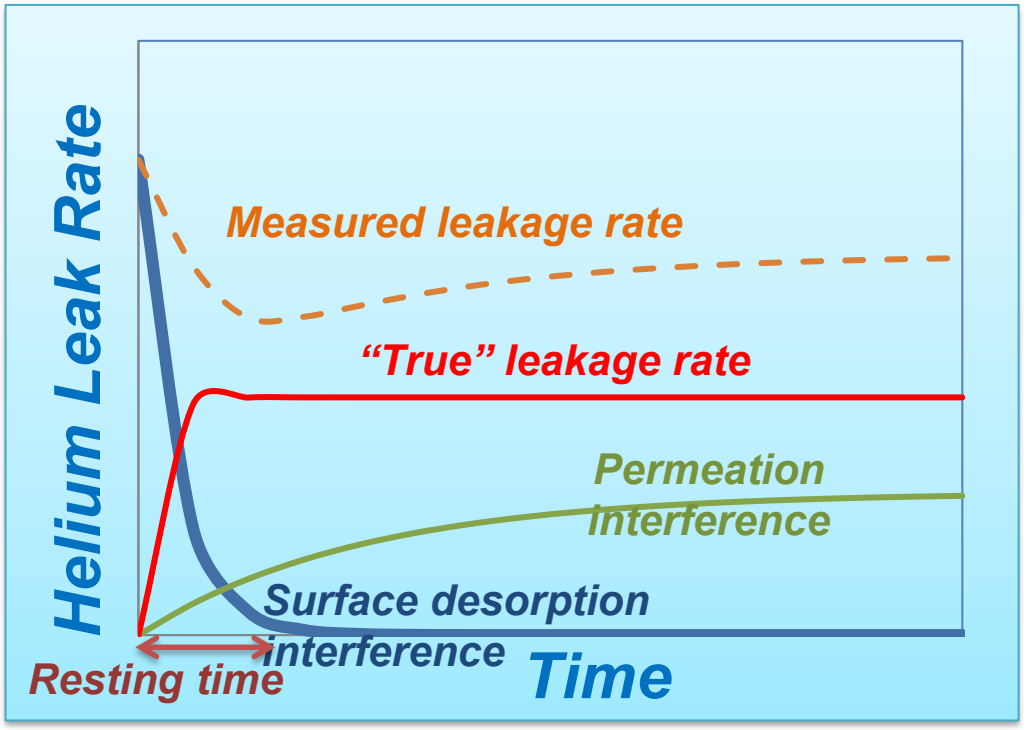
- A plunger rod is used to retain plunger during testing



Potential Interferences

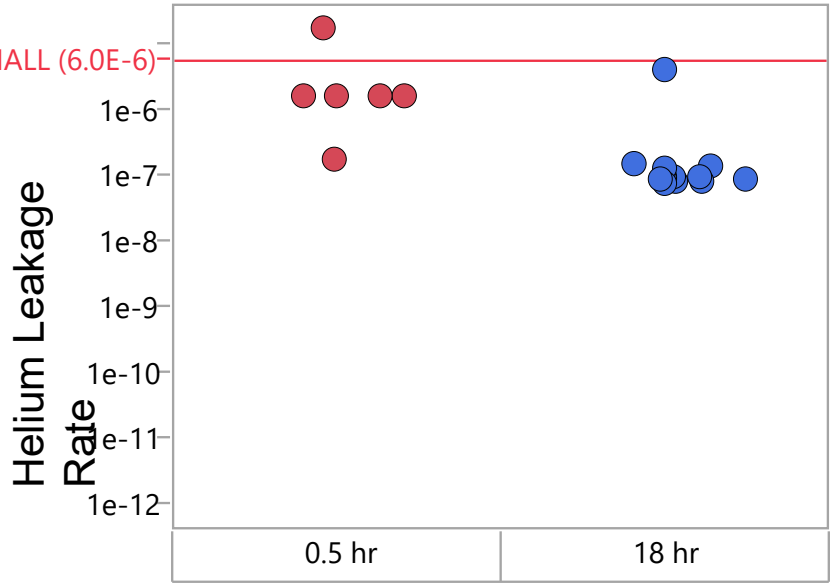
- **Desorption** of exterior surface-adsorbed helium
- Helium **permeation**





Preliminary Results

- ✓ **Estimated overall leakage rate**
  - Results can be artificially high due to surface desorption and permeation
- ✓ **Demonstrated conformance to MALL**



Improvement Needs

- ❑ Reduce helium background noise to measure "true" leakage rate
  - Exterior surface desorption
  - Permeation
- ❑ Need to evaluate sealing capability of critical seal elements and sub-systems

Method Improvement Strategy

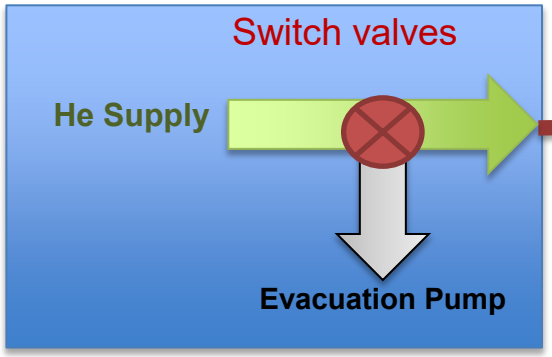
- ❑ "**Fast and Clean**" helium charging
  - **Fast**: allow testing to start prior to significant permeation
  - **Clean**: eliminate helium contact with interfering sample surfaces

- ❑ "**Divide and Conquer**" critical seal elements
  - Isolate critical seal elements for independent assessment

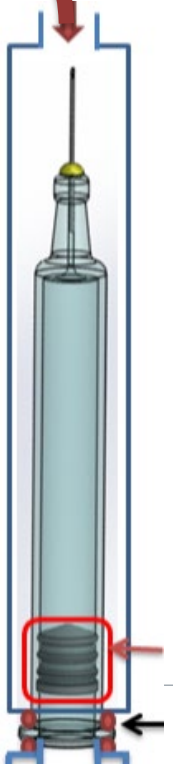
Key Enabler: Sample Fixture Design

Fast & Clean Charging of Helium

Goal: to achieve consistent 100% helium charging in the sample chamber to allow accurate quantitative leakage rate testing



Helium Charging Manifold

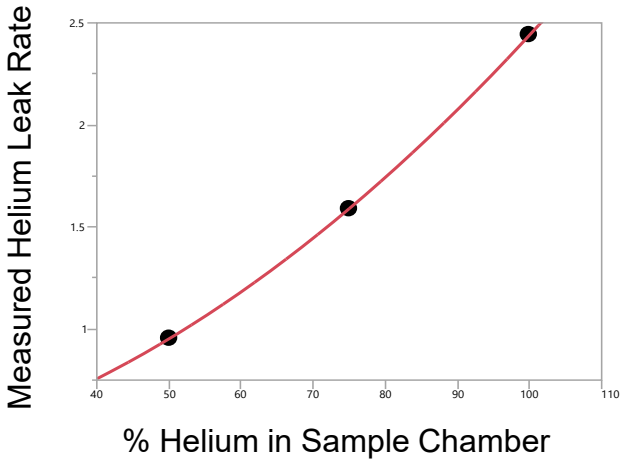


Sample Chamber

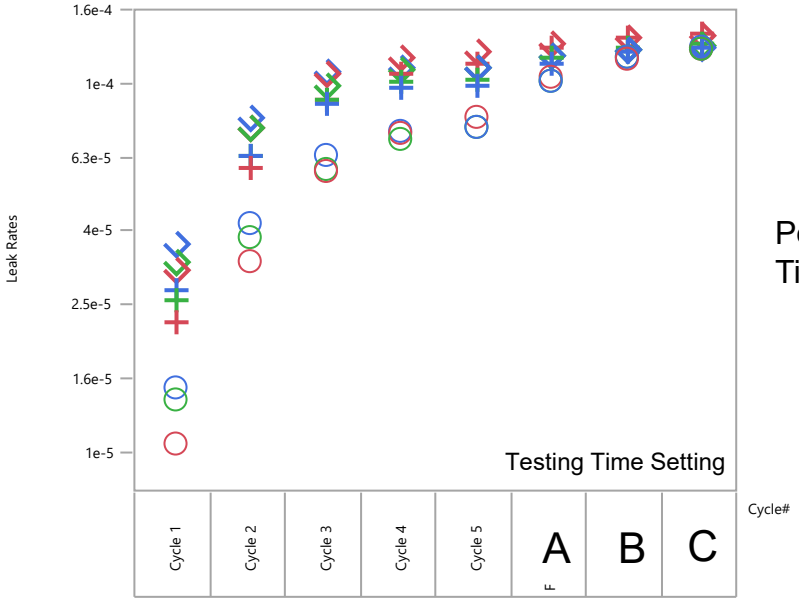
Manifold design regulates evacuation-helium backfill cycles to achieve fast and clean He charging

Optimize Helium Charging Parameters

Leakage Rates dependence on He% in Sample Chamber



Leakage Rates vs. Charging Parameters Study



Charging Parameter

Vac (s)	He (s)
6	12
8	16
10	20

Post-charging Test Time

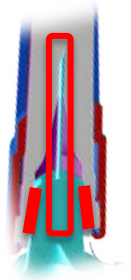
- A: 5 sec
- B: 10 sec
- C: 15 Sec

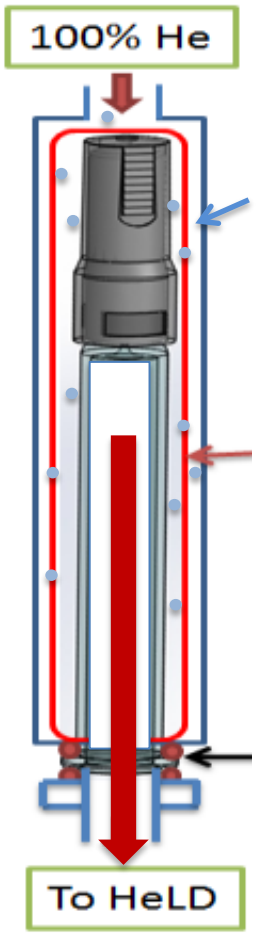
Measured leakage rate through a known leak

Key Parameters

- Charging cycle
  - Evacuation time (sec)
  - He back-fill time (sec)
- Number of Cycles
- Post-charging testing time (sec)

Testing Fixture Design

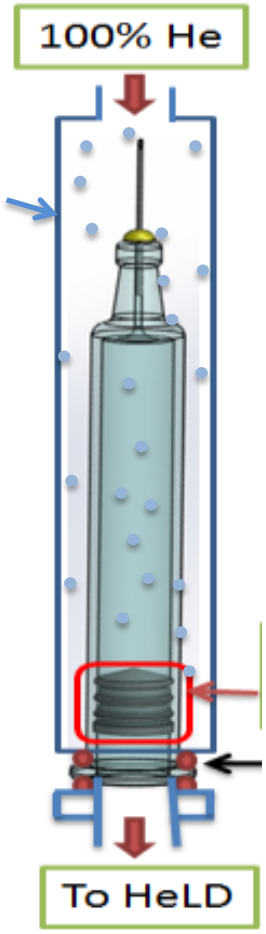




Sample Chamber (1 atm Helium)

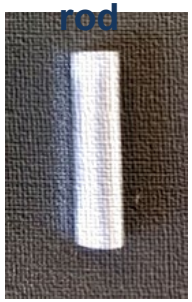
Mass Spec <0.01Torr

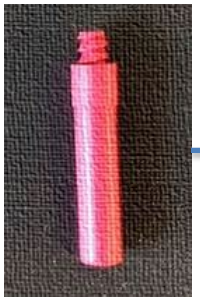
Needle Shield – Barrel Seal

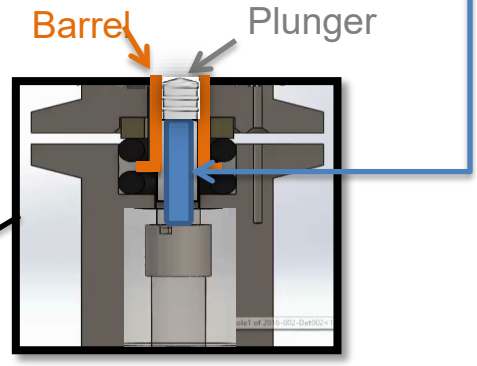


Plunger-Barrel Seal

Plunger Support

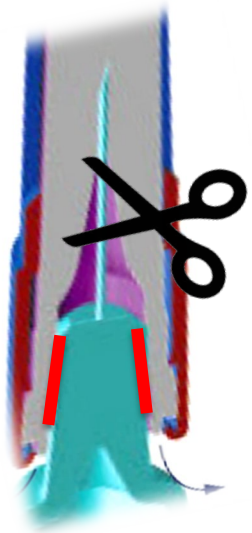


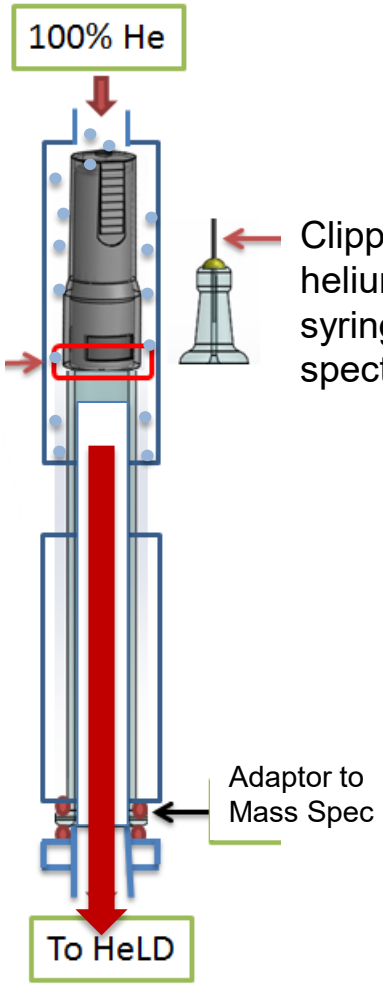




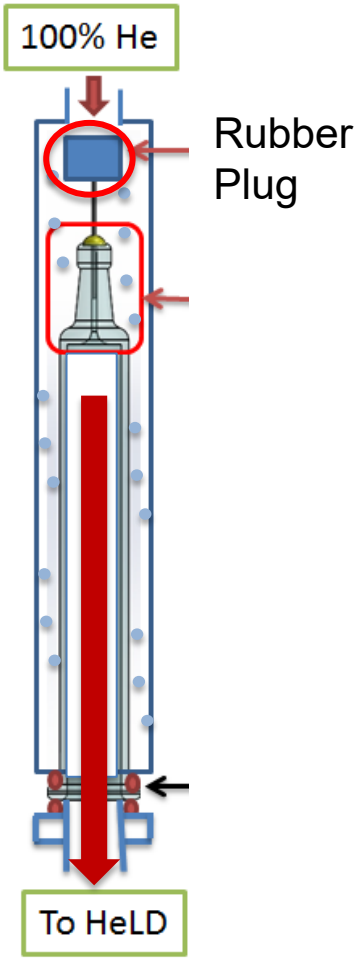
Two plunger support types based on common syringe injection device designs

Testing Fixture Design





Needle Shield – Barrel head Seal



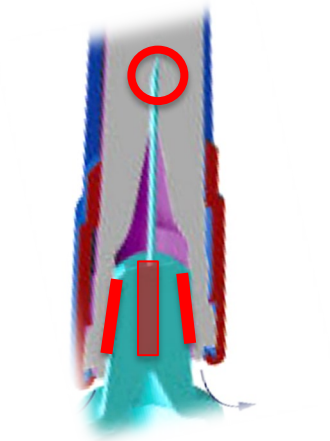
Needle Stem Seals

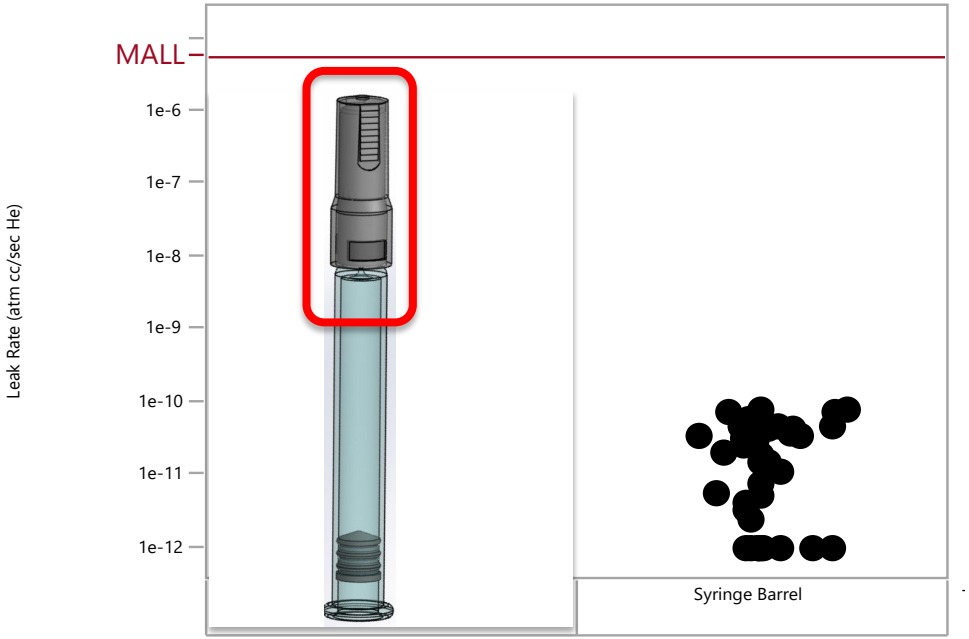
Evaluation of Needle Shield – Barrel Seal

A combination of 3 seal elements

- Needle shield – Syringe head
- Needle tip – Needle shield
- Glued staked needle

- Critical to product sterility and formulation content protection

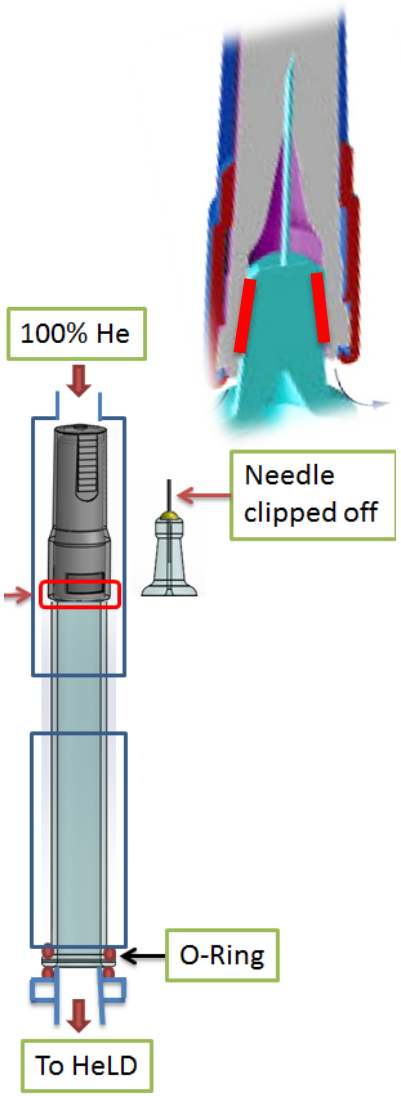




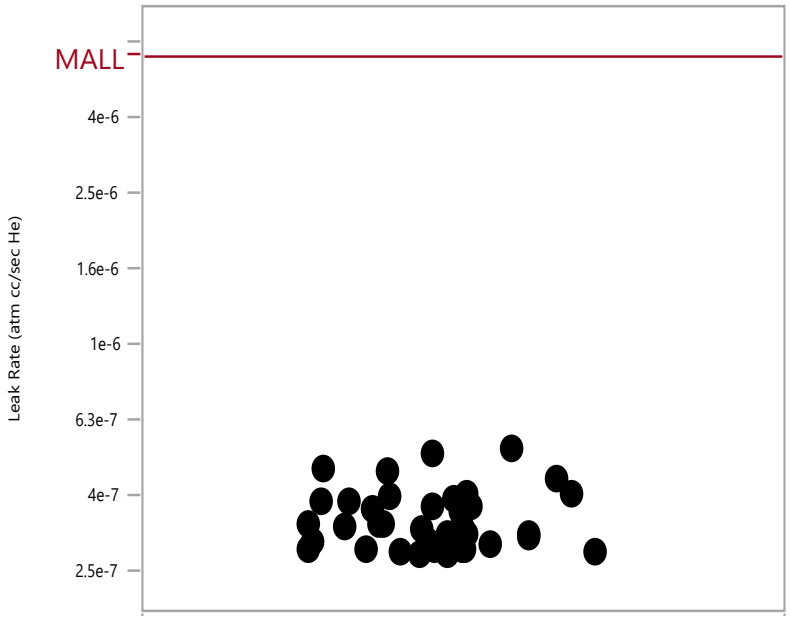
Leakage Rate <= 8 x 10^{-11} atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content

Evaluation of Needle Shield – Barrel Head Seal



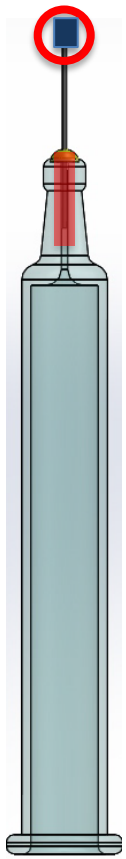
- **Physically mated (compression) seal**
  - Critical to needle stem sterility protection



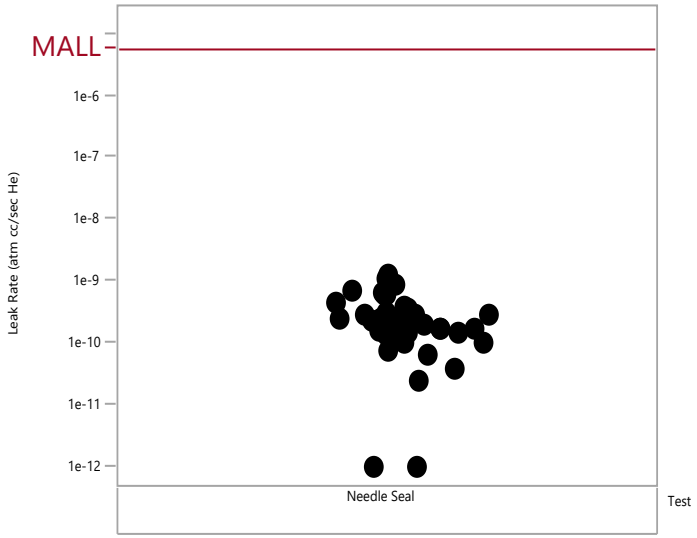
Leakage Rate <= 6×10^{-7} atm-cc/sec

- Confirm to MALL for preserving sterility

Evaluation of Needle Stem Seals



- Glued (physicochemically bonded) at the base
- Physically mated (compression) seal at the tip
  - Not definitive sterility barriers
  - Poor seals may result to product loss or injection issues



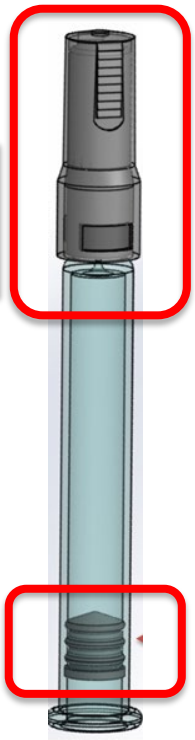
Leakage Rate <= $2x10^{-9}$ atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content

Inherent Package Integrity Summary

- DP compartment (Plunger & Needle Shield) <= 5 x 10^{-10} atm-cc/sec
- Needle stem compartment <= 6 x 10^{-7} atm-cc/sec
- All individual critical seals conform to MALL

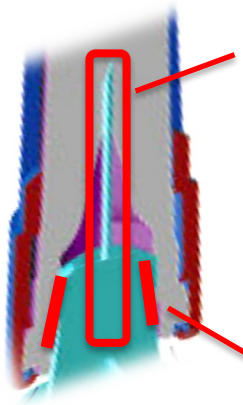
8x10^{-11} atm-cc/sec



4x10^{-10} atm-cc/sec

"Layered" seal design in needle shield significantly lowers overall leakage rate

– Added protection to drug product



2x10^{-9} atm-cc/sec

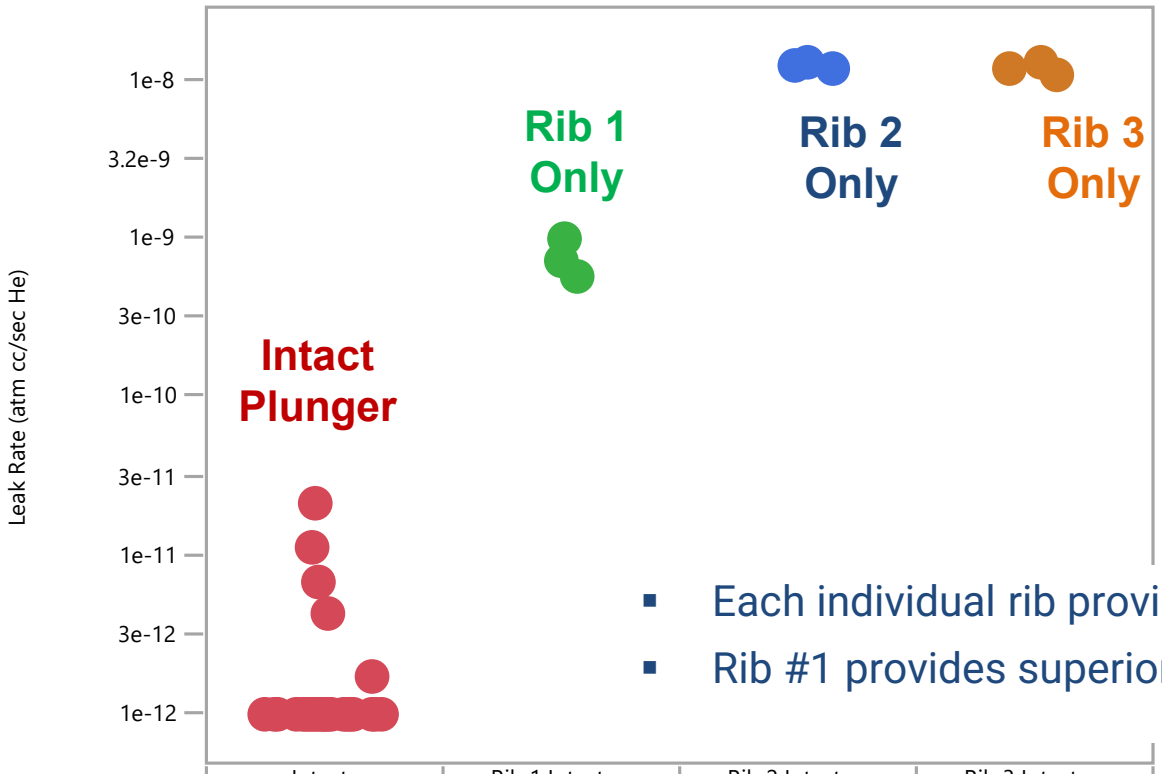
6x10^{-7} atm-cc/sec

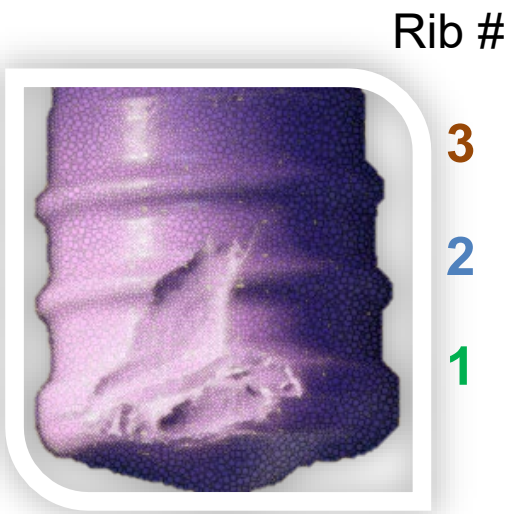
The needle shield – barrel head seal is the weakest among all seals

Package Integrity was verified for preserving sterility and formulation content

Design Robustness: Plunger Ribs

- Each plunger rib assessed individually for sealing capability
  - Assessed by compromising 2 of the 3 ribs, leaving 1 intact rib
  - Evaluate impact of potential plunger molding defects

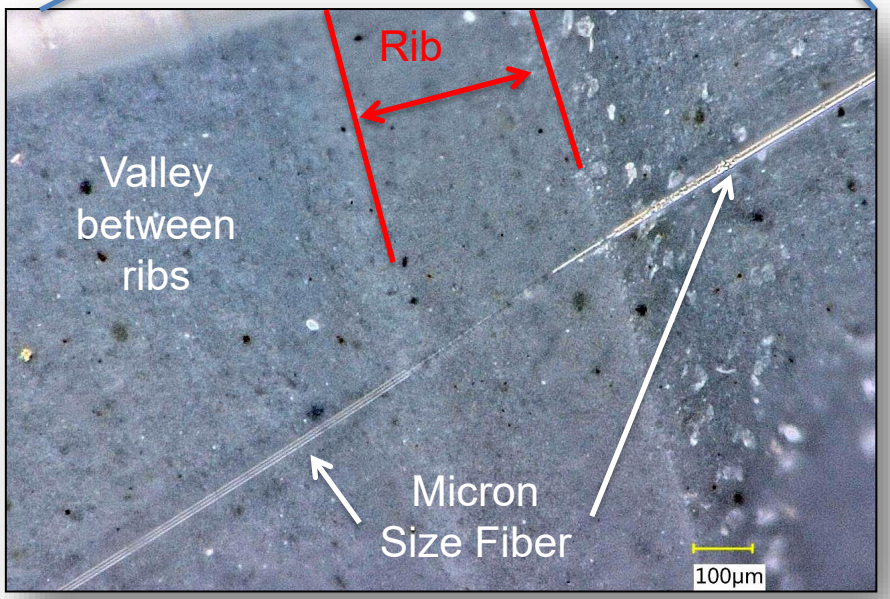




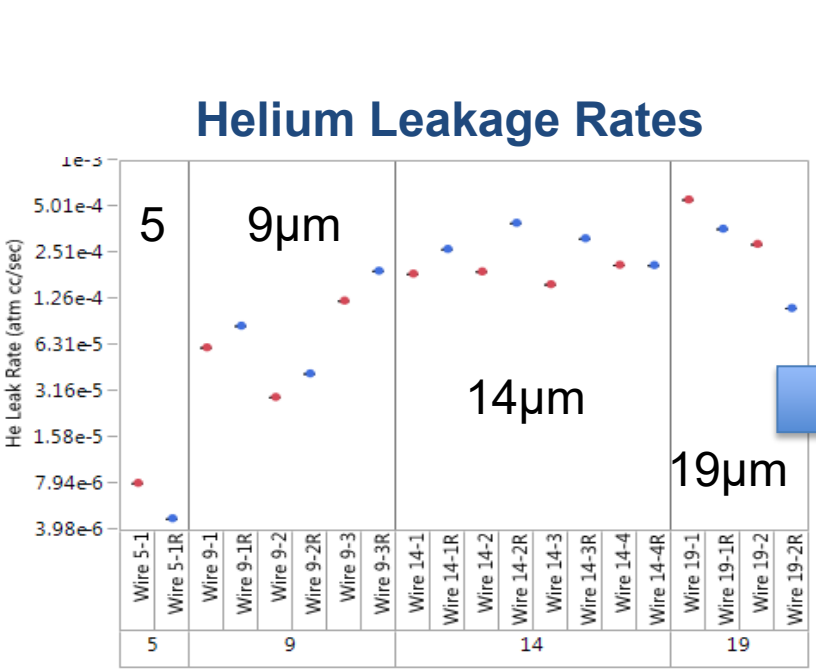
- Each individual rib provides adequate seal
- Rib #1 provides superior sealing performance

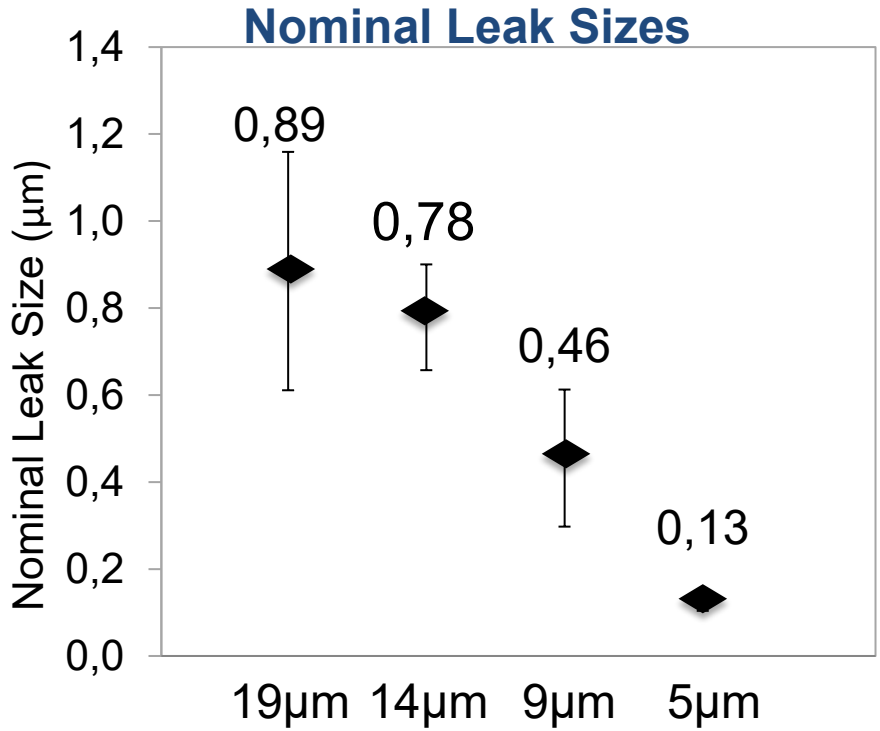
Design Robustness: Fiber Interference

- Fiber Intereference between plunger rib and barrel
- Industry needs a practical means to fabricate and characterize sub-micron size defects
- Assess impact of interfering fibers of various sizes



Design Robustness: Fiber Interference

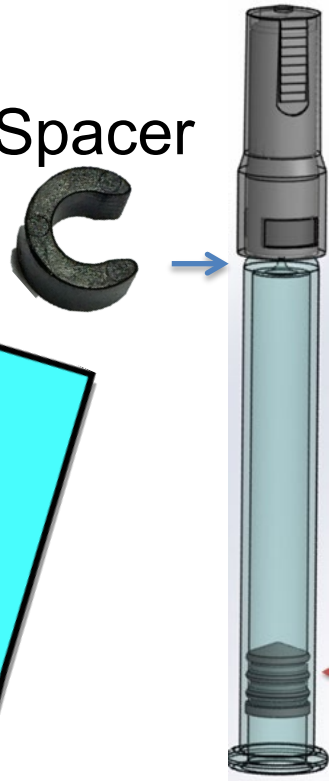




- Presence of interfering fibers could compromise plunger seal integrity
- Interfering fibers provide a practical means for fabricating sub-micron defects
  - Enable development of other CCI testing technologies

Potential Opportunities

Spacer



Needle Shield Gap Study

- How much needle shield movement until it leaks?
- Use spacer to create controlled gaps

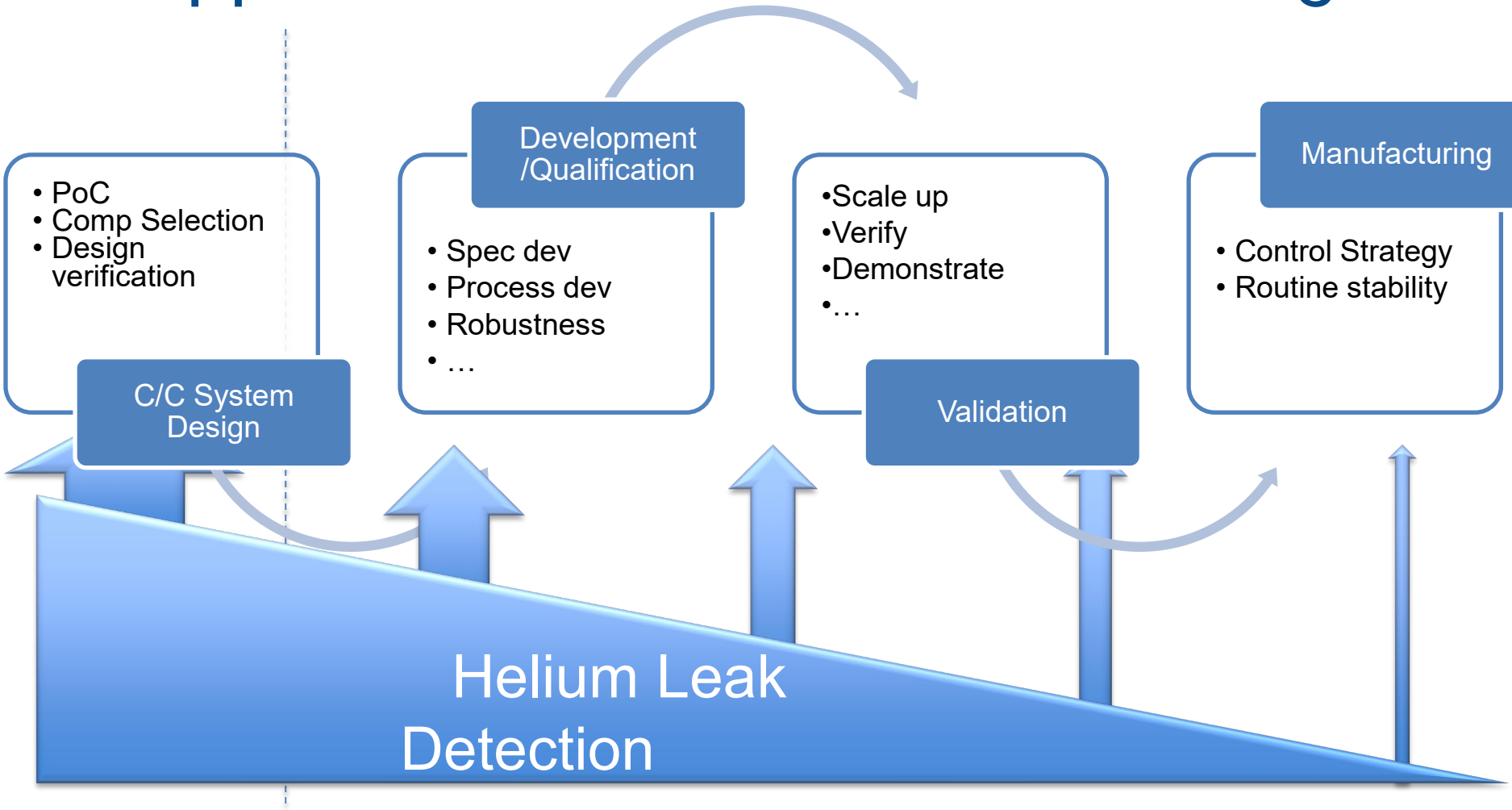
" CCI Capability"

- Multiple Lots
- Cpk of leakage rate?
- Correlation with dimensional Cpk

Component aging study

How does the seal performance change over time?

Application of Helium Leak Testing



Conclusions: Helium Leak Detection

- HeLD a capable CCI technology: sensitive, precise, and quantitative
  - Enable data-driven decision making: rich information; high throughput
  - Fixture design and helium charging critical for method development
- Inform container closure design and process development
  - Inform packaging component selection and system design
  - Assess container closure robustness against design, process variability
  - Demonstrate conformance to MALL
- Enable foundational CCI research
  - Characterize micron and sub-micron leaks

Acknowledgements

Eli Lilly and Company

Lei Li (co-author)
Li Liu (co-author)
Ross Allen
Lin Li
Jon Parker
Eric Jensen
Ron Iacocca
Andy Ratz
Galen Shi
Karthik Vaideeswaran
Craig Goldhammer

External Collaborators

Elmira Rad, Joseph Buckley, Mike Berger – Eurofins

Scott Damron & Jason Cumbee – AGY, Aiken, South Carolina